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Paracetamol poisoning in children and hepatotoxicity

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1 Paracetamol is one of the most common drugs that children accidentally ingest. Unlike the situation in adults, death and hepatotoxicity in children from paracetamol poisoning are exceedingly uncommon events. A review of the literature has revealed only seven deaths and fourteen cases of hepatotoxicity in children, with most of the cases resulting from chronic poisoning and not acute poisoning.
2 Children may be less prone to paracetamol hepatotoxicity because of developmental differences in the drug's metabolism and its pathways of detoxification. In the therapeutic setting of treatment of fever and pain in children, paracetamol is regarded as a drug with a higher therapeutic index, and as such, there seems to be little concern with strict adherence to dosage regimes.
3 Scrutiny of the above paediatric cases associated with chronic paracetamol poisoning suggests that the margin of safety of frequent therapeutic doses of paracetamol in infants and young children to be a lot lower than previously appreciated. This review highlights the need to re-evaluate the safety of paracetamol in the context of chronic therapy in infants and young children.

Keywords paracetamol poisoning children hepatotoxicity

Introduction

Paracetamol (*N*-acetyl-*p*-aminophenol) has been available over the counter in most countries since the late fifties (Meredith & Goulding, 1980). It is the preferred antipyretic and mild analgesic in children and has been advocated as an analgesic in adult patients with liver disease (Benson, 1983). In the late sixties reports of adult fatalities from acute paracetamol overdose (Binstone & Vys, 1968; Davidson & Eastham, 1966; Maclean *et al.*, 1968; Proudfoot & Wright, 1970; Rose, 1969; Prescott, 1966) established the association between paracetamol and hepatotoxicity.

Despite the advent of detoxifying agents in the 1970s, there were in Britain in 1984 176 deaths due to paracetamol poisoning alone and 305 deaths due to paracetamol taken with other drugs (Meredith *et al.*, 1986). Adults accounted for most of the serious and fatal cases. Young children represent a small proportion of significant paracetamol overdoses, and hepatic damage or death seems rare in this age group (Meredith *et al.*, 1978). In the North American National Multicenter Study (1976 to 1985) (Smilkstein *et al.*, 1988) there were 50 deaths from 11195 paracetamol overdoses, and 3.3% of all patients were under the age of 5 years. Of the 1067 patients at high risk of hepatic damage, 1.4% were in this age group. It is presumed that there were no deaths in this paediatric group, although this was not specifically reported.

As a result of this continuing 'epidemic', treatment of acute paracetamol poisoning has become commonplace. The most frequently employed agent is *N*-acetylcysteine, which is not in itself harmless (Dawson *et al.*, 1989; Flanagan *et al.*, 1987; Mant *et al.*, 1984). This has led us to review the situation pertaining to children, where hepatotoxicity seems infrequent and death exceedingly rare. We explore why this should be, and also whether it is in fact desirable for children to be treated. As this paper will demonstrate there are no absolute answers to these questions, hence the need to discuss the matter.

Diagnostic nomograms

When Mitchell and his colleagues (Jollow *et al.*, 1973; Mitchell *et al.*, 1973a,b, 1974; Potter *et al.*, 1973) reported the probable mechanism(s) for paracetamol hepatoxicity and that compounds with sulphydryl groups could prevent centrilobular necrosis in livers of laboratory animals intoxicated with paracetamol, the way was open for clinical trials with such sulphur containing compounds. Both Prescott *et al* (1976) and Rumack & Matthew (1975) produced nomograms of plasma paracetamol concentrations (logarithm) *vs* time (Figure 1) using the prognostic correlations obtained from adult data (Prescott

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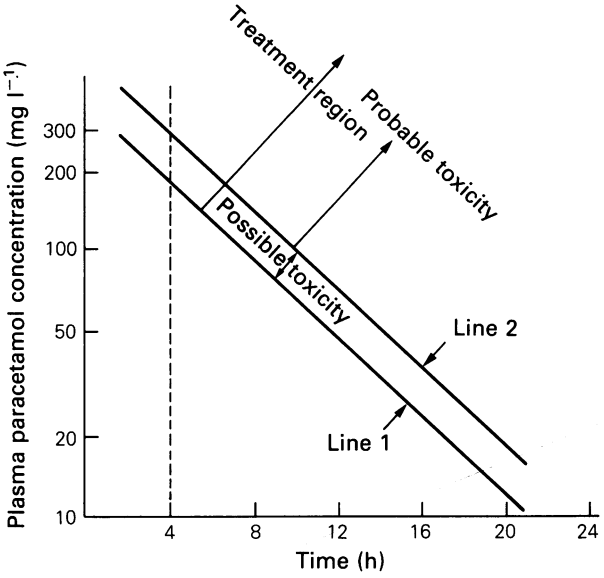

Figure 1 Nomogram for paracetamol poisoning, adapted from Prescott (1983).

et al., 1971). Treatment with these drugs was indicated when the plasma paracetamol concentration fell above line 1 in the nomogram (Figure 1). The slope of the line corresponded to a half-life of 4 h, and the 'intercept' at 4 h varied between 150 and 200 mg l^{-1}

Treatment

The two drugs advocated for the treatment of paracetamol poisoning are methionine (MET) and *N*-acetylcysteine (NAC). Although both can be given orally, only the latter can be given intravenously. NAC is the more commonly used drug and clinical studies over the past decade (Prescott, 1981; Rumack *et al.*, 1981; Smilkstein *et al.*, 1988) have shown that if the drug is given in appropriate doses within 16 h of ingestion to those patients who have plasma paracetamol concentrations above the nomogram 'treatment' line, or to those who have taken a potentially lethal dose (7.5 g or 150 mg kg^{-1}), the probability of cure is almost 100%. Prior to the availability of these drugs the mortality in all cases of paracetamol poisoning was 2–3% (Prescott, 1983). The risk of hepatic damage according to Pescott's nomogram (Figure 1) was 25–30% in the possible toxicity region, 60% in the treatment region and, 90% in the probable toxicity region (Prescott, 1983). Only 15–20% of poisoned patients were considered to be severely poisoned (Prescott, 1983; Smilkstein *et al.*, 1988).

Although NAC is thought to be relatively free from side effects, it may be associated with anaphylactoid reactions which usually occur within 1 h of starting an intravenous infusion (Dawson *et al.*, 1989). Three deaths have occurred with NAC, each after iatrogenic overdosage (Table 1). Sadly one 4 year old child who died, did not merit treatment with NAC according to the treatment nomogram. One adult (no. 3) had also taken prochlorperazine which may have contributed to his death.

Table 1 Fatalities from *N*-acetylcysteine treatment

Patient, age	*Clinical history*
1. 4 years (Editorial, 1984)	Paracetamol overdose, 1.8 g, Blood paracetamol level at 5 h, was 45 mg l^{-1}. NAC bolus given (2.17 g), infusion started (0.36 g h^{-1}; twice normal). Twenty minutes into infusion, developed cyanosis and hypotension – died, despite resuscitative measues.
2. 32 years (Mant *et al.*, 1984)	Paracetamol overdose. Blood paracetamol level at 12 h, was 145 mg l^{-1} NAC infusion (ten times normal dose) commenced. After two and a half to six times the normal dose was given, developed flushing and hypotension, was resuscitated, developed disseminated intravascular coagulation, and died 10 days later.
3. Adult (Mant *et al.*, 1984)	Paracetamol and prochlorpromazine overdose. Found unconscious at home. Blood paracetamol level 230 mg l^{-1}. Given ten times the loading dose (infused over 1.75 h) of NAC. Eight hours after admission had a cardiac arrest and died.

The problem in children

Although the nomogram is well-accepted for paracetamol poisoning in adolescents and adults, there has been some concern about children and also persons taking medications which induce hepatic microsomal enzyme activity. In children under the age of 5 years acute paracetamol toxicity is usually due to accidental ingestion. It may occasionally be due to attempted suicide in older children and is rarely due to intentional poisoning in infants (Hickson *et al.*, 1983, 1989). In Sydney the peak age group for children presenting with alleged toxic paracetamol ingestion over a 10 year period (1978–1988) was 2–3 years (Lim, 1989: unpublished data), which was similar to the Denver (1976–1984) (Rumack 1984) and the English experience (Meredith *et al.*, 1978). In Denver children under the age of 5 years represented 4.6% of 9000 cases of paracetamol poisoning. There was a general impression that children were less susceptible to the hepatotoxic effects of paracetamol than adults (Rumack, 1983). The Denver study (Rumack, 1984) revealed that young children had a lower incidence of clinical and biochemical hepatotoxicity at the same paracetamol levels as older children and adults. Vomiting is common in poisoned children and is one reason why many potentially toxic doses do not result in toxic blood levels (Rumack, 1984).

Seven deaths from paracetamol poisoning in young children have been reported in the literature (Table 2), their ages ranging from 2 to 72 months. Only one child was treated with NAC. Five of the children were given the drug by a parent for therapeutic effect at doses well above those recommended for age and weight. In four of them paracetamol was administered in divided doses over periods ranging from 1 to 6 days. Death due to accidental acute ingestion could only be entertained as a possibility in two cases, where the history of ingestion

Table 2 Fatalities in children from paracetamol poisoning

Age of patients (m = months)	*Clinical history*
	Chronic poisoning
40 m	Given 5.04 g paracetamol in divided doses over 24 h, under a physician's direction. Hospitalised at this time with abdominal pain and the serum paracetamol level 14 h after her last dose was 54 mg l^{-1}. Discharged on day 2, and readmitted on day 3, obtunded and with biochemical evidence of severe hepatic damage. She died some time later, despite supportive therapy (Nogen & Gremner, 1978).
24 m	Prescribed paracetamol suppositories for antipyresis and given 17 doses over 70 h (11.05 g). Hospitalised because of lethargy, and found to be in hepatic failure. She died on day 3. The blood serum paracetamol level 24 h after the last dose was 25 mg l^{-1} (Clark *et al.*, 1983).
36 m	Mother gave child 500 mg paracetamol suppositories (51 mg kg^{-1} dose) every 3 h for a febrile illness which was present for 6 days. Presented in hepatic coma, and died 5 days later (De-Nardo *et al.*, 1988).
72 m	Child had measles, and was given paracetamol for antipyresis. Initially 325 mg given six hourly, with progressive increase in dose over the next 3 days. Hospitalised with abdominal pain and the serum paracetamol level 11 h after the last dose was 63 mg l^{-1}. The paracetamol half-life was 15 h. Despite adequate treatment with NAC she developed hepatic and renal failure, and died on the 11th day (Blake *et al.*, 1988).
	Acute poisoning
2 m	(Abstract) Given 16.5 times the recommended paracetamol dose, rectally. Phenobarbitone was also given. Died, with evidence of hepatic and renal insufficiency (Cabrera *et al.*, 1982).
	Dosing regime not known
36 m	Registrar General's statistics for England and Wales in 1970, with documented 'paracetamol levels' at postmortem examination (Rumack & Matthew, 1975).
13 m	Hospitalised with vomiting and lethargy, lapsing into coma soon afterwards. Developed liver failure on day 2. She died on day 5. At postmortem, the blood paracetamol level was 31 mg l^{-1} (Weber & Ernest, 1980).

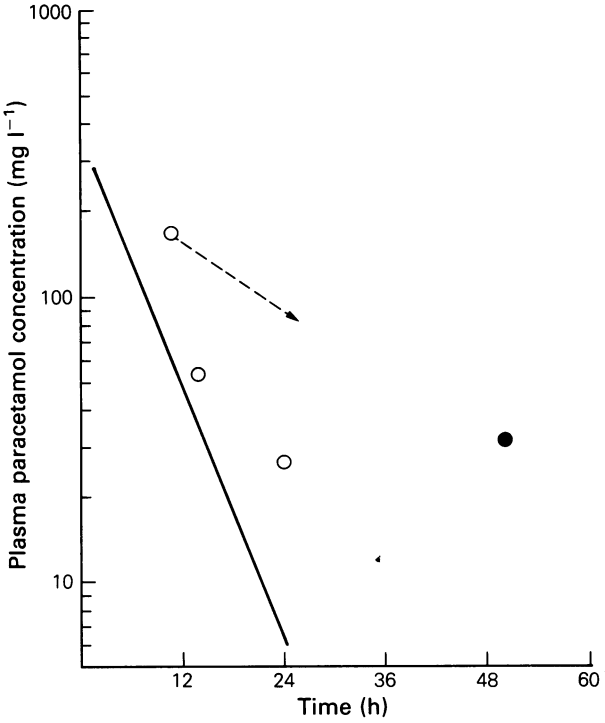

Figure 2 Plasma paracetamol concentrations from children who have died from paracetamol poisoning (see Table 2). Open circles represent chronic ingestions, and the closed circle represents the last case in Table 2 where the dosing regime is not known. The drawn line represents the treatment line (line 1 in Figure 1) and the dashed line represents the half-life of paracetamol in the particular case.

was not reported or known. Serum paracetamol concentrations were performed in four cases and were all above the treatment line (Figure 2). As can be seen death due to accidental acute ingestion of paracetamol in young children seems extremely rare.

In addition to the above deaths, there are a number of reports of paracetamol poisoning in children leading to severe liver damage, diagnosed histologically or biochemically (Table 3). Not included in Table 3 are three children in the Denver study (Rumack, 1984) who were aged less than 12 years, had toxic paracetamol plasma levels, and had elevated hepatic transaminase levels consistent with severe hepatic damage. It is presumed that poisoning was due to acute ingestion. Treatment with oral NAC was begun more than 16 h after ingestion in each of the three children. Of the eleven cases in Table 3 three were also due to acute ingestion. Case 11 was treated with NAC at 8 h. The other eight infants had been administered between 60 mg and 420 mg kg^{-1} day^{-1} of paracetamol over periods ranging from 2 days to 1 month (reputedly for therapeutic purposes). Figure 3 shows the paracetamol concentrations in relation to the treatment line. Although case 5 had concentrations below the treatment line the elimination half-life of paracetamol was greater than 4 h. The recommended daily dose for paracetamol in children is 90 mg kg^{-1} given 4 or 6 hourly (Frank & Coulthard, 1988; Temple, 1983; Wilson *et al.*, 1982). Although the optimum paediatric dose for antipyresis is 20 mg/kg (Petersen 1985; Temple, 1983; Wilson *et al.*, 1982) this dose should only be used as a loading dose if repeated administration is envisaged, with subsequent maintenance doses being in the range of 10–15 mg kg^{-1} (Wilson *et al.*, 1982). It is our impression that in recent years doses of 15 to 20 mg kg^{-1} every 4 h have been prescribed in children to treat antipyresis. If case 6 is ignored, the mean dosage kg^{-1} day^{-1} for the other six cases of chronic poisoning is about 130 mg kg^{-1} day^{-1}. This would suggest that in chronic therapy in young children, especially infants, the therapeutic index for paracetamol in relation to hepatic

Table 3 Liver damage in children from paracetamol poisoning

No.	*Age*	*Sex*	*Weight (kg)*	*Dosage regime*	*[P]*	*T*	R_x	*Comment*	*Reference*
				Chronic poisoning					
1	19 m	F		19 g in 7 days	?	?	?		Calvert *et al.* (1978)
2	7 w	F		30 mg oral, 4–6 hourly, 6–8 days, approx 60 mg kg^{-1} day^{-1}	54	11	N	Above R_x line	Greene *et al.* (1983)
3	6 w	M		50 mg oral, 4 hourly, 2 days approx 100 mg kg^{-1} day^{-1}	119	12	Y	Above R_x line	Greene *et al.* (1983)
4	15 m	M	13.4	80–320 mg/day for 1 month, then 1 to 2 g daily for 2 w, then 2g daily for 4 days, 150 mg kg^{-1} day^{-1}	0	30	N		Agran *et al.* (1983)
5	18 m	F	9.8	120 mg oral, 2 hourly, 2 days 147 mg kg^{-1} day^{-1}	14	36	N	Above R_x line	Swetman *et al.* (1984)
6	7 m	M	8.5	325 mg supp. 6 hourly, 12 doses (3.9 g), 152 mg kg^{-1} day^{-1}	72 22	4 16	N	Below R_x line $t_{½} > 4$ h	Smith *et al.* (1986)
7	11 m	F	9.3	650 mg supp. 4 hourly, 8 doses (5.2 g) 420 mg kg^{-1} day^{-1}	240 < 5	11 > 36	N	Above R_x line	Henretig *et al.* (1989)
8	22 m	F	12.5	650 mg supp. 10 doses over 3 days 174 mg kg^{-1} day^{-1}	30 24	20 32	Y	Above R_x line $t_{½} > 4$ h	Henretig *et al.* (1989)
				Acute poisoning					
9	38 m	F	14.2	Acute ingestion 11.4 g	94 26	24 48	N	Above R_x line $t_{½} > 4$ h	Arena *et al.* (1978)
10	36 m	M	13	Acute ingestion 3 g	?	?	?	?	Czajka *et al.* (1982)
11	12 m	M		Acute ingestion 10 g	863	5	Y	Above R_x line $t_{½} > 4$ h	Lieh-lai *et al.* (1984)

Liver damage was assessed to be present if histology showed centrilobular necrosis or serum transaminase levels were significantly elevated
(SGOT > 1000 iu/l). The dosage regimes in cases 2 and 3 were calculated from the paracetamol formulations referred to in the article. Cases 1 and 10 were cited in articles by Prescott (1986), and Agran *et al.* (1983). Wt. refers to the body weight in kilograms. m = months. w = weeks. [P] = serum or blood paracetamol concentrations, mg l^{-1}. T = time (hours after ingestion) when [P] taken. R_x = treatment with NAC (Y = treatment, N = no treatment). Above R_x line refers to line 1 in Figure 1.

toxicity is low. In adults hepatotoxicity following the therapeutic use of paracetamol usually occurs in the clinical setting of chronic alcoholism and chronic excessive dosage (Benson, 1983; Prescott, 1986).

Paracetamol hepatotoxicity

Paracetamol is metabolised extensively by the liver (Figure 4) via three main pathways; sulphation, glucuronidation and oxidation (Mitchell *et al.*, 1974). The first two pathways are quantitatively more important than the last, but the oxidative pathway is the culprit as far as toxicity is concerned (Mitchell *et al.*, 1973a). The oxidative pathway produces two conjugated compounds P(paracetamol) cysteine and P-N-acetylcysteine (P-mercapturate) (Davis *et al.*, 1976). There are marked inter-individual differences in the pathways with differences in the sulphation and glucuronidation pathways being as great as 3 fold, and as high as 60 fold in the oxidative pathway (Critchley *et al.*, 1986). In adults the glucuronide conjugate accounts for 60% of metabolites found in urine, the sulphate 35%, and the oxidative conjugates 5%. The ratio of glucuronide to sulphate conjugates in urine in adults is between 1.8 and 2.3 (Alam *et al.*, 1977; Cummings *et al.*, 1967; Millter *et al.*, 1976). In neonates this ratio is about 0.35 (Levy *et al.*, 1975; Miller *et al.*, 1976), in children aged 3–10 years 0.8 (Alam *et al.*, 1977; Miller *et al.*, 1976) and in young adolescents 1.61. The oxidative pathway has been studied in neonates (Lederman *et al.*, Notarianni *et al.*, 1987; Roberts *et al.*, 1984) and the oxidative metabolites account for 10 to 20% of paracetamol products in urine. Human fetal cells (Rollo *et al.*, 1979) can oxidise paracetamol, although at a slower rate than the adult liver. Although this pathway has not been studied in young children, it is reasonable to assume that the oxidative pathway exists in these children and that its activity is somewhere between that seen in neonates and in adults.

Oxidation of paracetamol occurs in the hepatic microsomes primarily catalysed by cytochrome P_{450} (Potter *et*

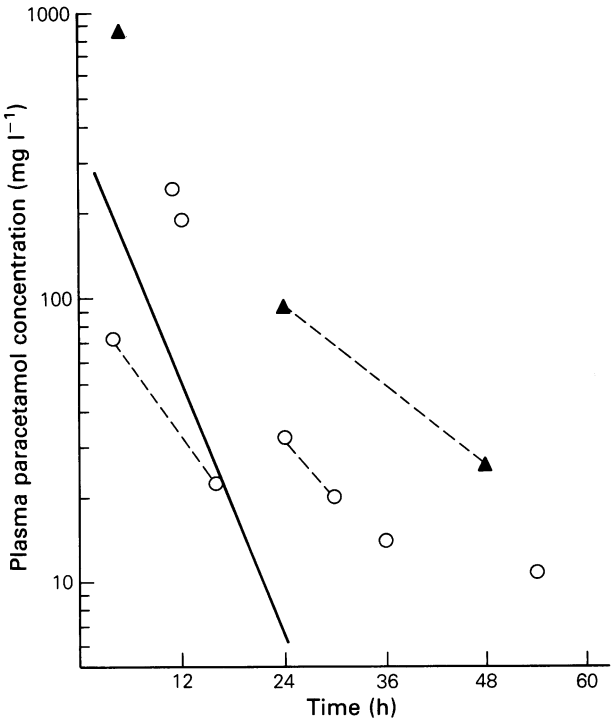

Figure 3 Plasma paracetamol concentrations from children who had severe liver damage from paracetamol poisoning (see Table 3). Open circles represent chronic ingestions, and the closed triangles represent acute ingestions. The drawn line represents the treatment line (line 1 in Figure 1) and the dashed line represents the half-life of paracetamol in the particular cases.

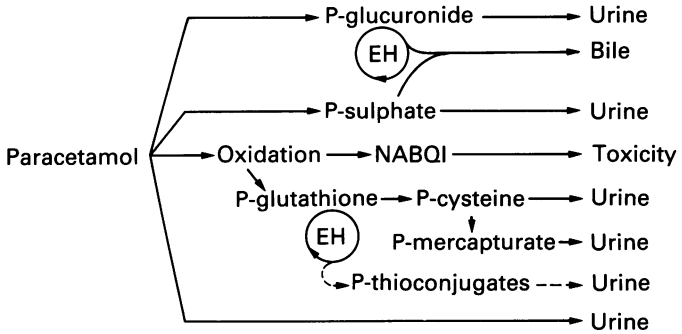

Figure 4 Paracetamol metabolites and routes of excretion. P = Paracetamol, EH = Enterohepatic cycle, NABQI = *N*-Acetyl Benzoquinineimine. The thioconjugates are very minor metabolites of paracetamol (Aguilar *et al.*, 1988; Klutch *et al.*, 1978).

al., 1973). The process produces a highly reactive arylating compound called N-acetyl benzoquinoneimine (NABQI). This compound is normally rapidly conjugated to glutathione from which the oxidative conjugates (Figure 4) are derived. Glutathione may also reduce NABQI back to paracetamol (Davis, 1986). As long as the rate of formation of this toxin is not greater than the maximal rate of synthesis of glutathione there will be no damage to the cell and organ. A number of studies in adults have shown that the sulphate pathway can become saturated at relatively low doses (0.5 to 3 g) (Clements *et al.*, 1984; Slattery *et al.*, 1987), and that depletion of the sulphate consubstrate for this pathway can occur during multiple dosing with therapeutic doses of paracetamol (Hendrix-Treacy *et al.*, 1986). In overdose both the sulphate and glucuronide pathways are saturated (Davis *et al.*, 1976; Slattery & Levy, 1979). There is some debate whether the glutathione pathway can be saturated, but the consensus is that there is a time-dependent depletion of glutathione as this pathway is taxed during an overdose (Slattery *et al.*, 1987). As a result the percent excretion of the sulphate and glucuronide conjugates in the urine falls and the percentage of oxidative compounds increases. In summary, acute paracetamol overdose leads to saturation of the sulphation and glucuronidation pathways, which in turn increases traffic through the oxidative pathway. If this is not matched by a similar sustained increase in glutathione stores (Mitchell *et al.*, 1973b), it leads to unconjugated NABQI which is free to destroy the cell.

If the oxidative pathway is more active in young children than in adults, as is thought to be the case with other drugs, the detoxifying pathways may be more efficient. This could account for the apparent reduced acute toxicity of paracetamol in children. Supporting evidence comes from mice, as young mice have 4 fold greater glutathione turnover (Lauterburg *et al.*, 1980) and increased activity of the glutathione peroxidase/reductase enzyme system (Adamson & Harman, 1989) than older mice and are less susceptible to paracetamol toxicity.

For ethical reasons it would not be possible to evaluate the saturability of the sulphate or glucuronide pathway in young children, although information could be obtained from children receiving paracetamol therapeutically. After repeated therapeutic doses (12–14 mg kg^{-1} 4 h^{-1} or 22–27 mg kg^{-1} 8 h^{-1}) in 10 febrile paediatric patients (mean age 1.1 years, range 0.5–6.4 years) there was a trend towards increased serum paracetamol concentrations at steady state as compared with levels obtained after the first dose (Nahata *et al.*, 1984). Although a time-dependent increase in bioavailability could explain this finding, it seems more likley that there is time-dependent decrease in paracetamol clearance. In rats (Galinsky & Levy, 1981) there is a time-dependent decrease in paracetamol elimination during intravenous infusion of paracetamol due to consubstrate (sulphate) depletion. Using the data of Nahata *et al.*, (1984) a significant negative correlation was present between percent increase in AUC (steady state compared with single dose) and age ($r^2 = -0.56$, $P = 0.02$) after excluding one outlier. This suggests that a reduction in paracetamol clearance with chronic dosing is more likely to occur in younger infants, possibly as a result of consubstrate depletion and saturation of a conjugating pathway (sulphation). As a result increased oxidative metabolism may occur, necessitating adequate glutathione stores to conjugate with the toxic metabolite. Administration of therapeutic doses of paracetamol to adults increases glutathione turnover (Lauterburg & Mitchell, 1987) and chronic paracetamol dosing in mice decreased hepatic glutathione levels (Reicks & Hathcock, 1989).

These findings suggest that chronic paracetamol ingestion in very young infants may lead to depletion of cosubstrates required for detoxification of the drug and consequently increase the likelihood of hepatotoxicity.

This is more likley to occur when higher than recommended doses are given regularly as in the cases described in Table 3. The extra stress of illness, whether associated with fever or not, may also effect hepatic glutathione stores and needs to be evaluated in the context of long term therapy with paracetamol. With accidental acute paracetamol poisoning in young children the likelihood of severe hepatotoxicity or death is very low, even when toxic doses are ingested. As alluded to earlier this may be due to differences in paracetamol metabolism and detoxification as compared to adults. In view of the potential for intravenous NAC to cause life-threatening adverse reactions, preference should be given to using oral NAC in children when indicated. The therapeutic use and metabolism of paracetamol in infants and young children should be reassessed with stringent guidelines for dosage regimes adhered to. The possibility that raised hepatic transaminase levels in an ill child may be due to aggressive use of paracetamol should always be kept in mind.

In conclusion, the present paediatric guidelines for the treatment of acute paracetamol poisoning and for antipyretic and analgesic therapy with paracetamol if adhered to, should be safe and efficacious. In addition, the degree of safety of chronic paracetamol therapy should be reassessed in infants and young children in studies similar to Nahata *et al.*'s (1984). The studies should attempt to look at the complete metabolic profile of paracetamol after single and multiple doses, and if possible to make an evaluation of glutathione turnover before and during paracetamol therapy.

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